Remarks

Claims 60, 61, and 69 (renumbered 58, 59, 67, respectively) are pending after the cancellation of claim 68 (renumbered 66) herein. Claims 60, 61 and 69 are amended with support in the application and claims, and as further described below. New claims 68, 69 and 70 are added.

The specification is amended to recite "body sample" by amendment to page 35 of the specification, where the language of a portion of claim 60 clause b is recited. This amendment is supported in claim 8 as filed and in claim 60, and also in the specification as filed at page 35, line 5.

The claims that refer to the 423 nucleotides set forth in Figure 1 have been amended to recite the sequence from Figure 1 as supported Figure 1.

Support for the amendments to claim 58 are found in the teaching regarding mammary (breast) carcinoma. Recitation of detection of mRNA is supported by reference to the detection of a single transcript in A431 cells in the parent application (p. 21, lines 16-17).

New claim 68 corresponds to claim 58, but is directed to the detection of increased expression. Support is found in the claims as filed and in the specification where a method of detecting increased expression is described. For example Fig. 6 "shows the overexpression of MAC117 in RNA in human mammary tumor cell lines ... Total cellular RNA (10 μg) of mammary tumor cell lines, normal fibroblasts M413 and HBL100 was hybridized with a cDNA probe derived from the 5' end of the coding region (Fig. 5B, probe a)..." Furthermore, the description of Fig. 8 states that it shows the gene amplification of MAC117 in 4 mammary tumor cell lines and the absence of MAC117 gene amplification in 4 other mammary tumor cell lines overexpressing MAC117 mRNA.".

Support for detection of an increase in antibody binding, is implicit in the description of the antibodies and kits in the overexpression/increased expression context in the present application and the parent application.

New claim 69 corresponds to claim 59, but is directed to the detection of increased expression of MAC117. Support is as noted above for claim 68 and in the claims as filed and in the specification where a method of detecting increased expression is described.

New claim 70 corresponds to claim 67, but is directed to detection of increased expression of MAC117. Support is as noted above for claim 68 and in the claims as filed and in the specification where a method of detecting increased expression is described.

Interview Summary

Applicants appreciate the in person interview granted by Examiner Rawlings on February 25, 2009. The claims were discussed in detail and potential amendments to address the examiner's concerns were discussed. The above amendments and the following remarks follow the discussion with Examiner Rawlings.

Numbering of the Claims

The Examiner has stated that "[i]t appears that claims numbered 16 and 17 were never added; thus, claims 18-69 are currently misnumbered." The Examiner has further stated that "Applicant is advised to remedy this deficiency in replying to this Office action by submitting a set of claims in which the claims are properly numbered in consecutive order." As such, Applicants have renumbered the claim numbers in this Response. The Applicant agrees with the Examiner's renumbering of claims 18-69 as claims 16-67.

In applicants' the remarks below, the renumbered claim numbers are referred to parenthetically.

Priority

The Office Action states that applicant's claim under 35 U.S.C. §§ 119(e) and/or 120, 121, or 365(c) for benefit of the earlier filing date of Application No. 06/836,414, filed March 5, 1986, is acknowledged. In this regard the Office Action further states the following:

> However, claims 60, 61, 68, and 69 do not properly benefit under §§ 119 and/or 120 by the earlier filing dates of the priority documents claimed, since those claims are rejected under 35 U.S.C. § 112, first paragraph, as lacking adequate written description and a sufficiently enabling disclosure. To receive benefit of the earlier filing date under §§ 119 and/or 120, the later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994). See M.P.E.P. § 201.11.
>
> Accordingly, the effective filing date of the claims is deemed the filing date of the instant application, namely October 21, 1987.

Applicants note the Office Action does not state in this rejection what subject matter claimed in claims 60 (58), 61 (59), 68 (66) and 69 (67) is not disclosed in Application No. 06/836,414. However, the Office Action alludes to the rejection under 35 U.S.C. § 112, first paragraph. For the reasons stated in response to that rejection, the present rejection is also believed to be overcome.

Furthermore, the specification of the priority application is co-extensive with the disclosure of King et al. (Science 1985, Sept. 6, 229:974-976). King is cited by the Office as anticipating claims 60 (58) and 61 (59). Applicants traverse this rejection for the reasons stated below. However, by making both the present rejection and the rejection for anticipation, the Office is taking inconsistent positions. In order to anticipate a claim a reference must enable what is claimed and must describe what is claimed (except in the context of inherency). Thus, if the Office views a reference as anticipatory of the presently pending claims, and the priority application specification is co-extensive with the disclosure of the reference, the priority application specification must meet the requirements of 35 U.S. C. § 112, first paragraph.

Drawings

The drawings are objected to because they depict nucleotide or amino acid sequences that are not identified by sequence identifiers. In this regard the Office Action further states the following:

> The drawings set forth as Figures 1 and 3 are objected to because the figures depict nucleotide and/or amino acid sequences, which are not identified by sequence identification numbers, either in the figure or in the brief description of figures beginning at page 5 of the specification, as originally filed. The Office Actions states that sequences appearing in the specification and/or drawings must be identified by a sequence identifier in accordance with 37 C.F.R. 1.821(d); sequence identifiers for sequences appearing in the drawings may appear in the drawings or in the brief description of the drawings.
>
> A replacement drawing sheet, including the correction, is required, if the drawings are objected to. See 37 CFR 1.121(d). However, this ground of objection would be withdrawn, so that a replacement drawing would be not be required, if Applicant were to amend the brief description of the figures beginning at page 5 of the specification to include sequence identification numbers.

Applicants note that the present application was filed prior to the May 1, 1990 final rulemaking publication of 37 C.F.R. 1.821(d). Thus, this rule does not apply to the present application. According to the MPEP 6th Edition, Revision 2, Section 2421.01, "[f]or the purposes of the sequence rules, the term "new" with regard to applications means: -For regular US applications, the application must have been filed on or after October 1, 1990. Continuing applications that claim a date prior to October 1, 1990, under 35 U.S.C. 120, except continuations-in-part (CIPs) filed on or after October 1, 1990, where material added includes a sequence, are not new applications." Similarly, the Final Rule for Requirements for Patent Applications Containing Nucleotide Sequence and/or Amino Acid Disclosures published in the Official Gazette at 1121 O.G. 82 (June 23, 1998) states that "[s]ections 1.821 through 1.825 as amended apply to applications filed on or after July 1, 1998, except for: (1) applications that claim the benefit of a prior application under 35 U.S.C. 120 filed before July 1, 1998, and which do not add subject matter involving a sequence listing subject to 1.821 through 1.825..." Thus, since this application was filed before October 1, 1990, it is not subject to the sequence rules set forth in sections 37 C.F.R. § 1.821 through 37 C.F.R. §1.825. Thus, this rejection is believed to be inapplicable to the present application, and its withdrawal is respectfully requested.

Objections to the Specification

A. The specification is objected to because the use of improperly demarcated trademarks has been noted in this application. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks. See MPEP § 608.01(v).

Amendments to the specification have been made to overcome this objection. In particular, the paragraph beginning on page 15, line 15 and the paragraph beginning on page 17, line 2 were replaced as requested by the Examiner to indicate the trademark status of SPEEDVAC and PACKAGENE. In view of these amendments, withdrawal of this rejection is believed to be merited and is respectfully requested.

B. The disclosure is objected to for the following reason: The specification contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). Sequences appearing in the specification and/or drawings must be identified by sequence identifier in accordance with 37 C.F.R. 1.821(d). According to 37 CFR § 1.821(a), an unbranched sequence of four or more specifically identified amino acids or an unbranched sequence of ten or more nucleotides must be identified by sequence identification numbers. See MPEP § 2422.01.

For the reasons stated above, applicants are not required to provide a sequence listing.

C. The specification is objected to because the pages are not numbered consecutively in accordance with the requirements set forth under 37 C.F.R. § 1.1521, which states: "Other than in a reissue application or reexamination proceeding, the pages of the specification including claims and abstract must be numbered consecutively, starting with 1, the numbers being centrally located above or preferably below, the text." M.P.E.P. § 608.01.

Amendments to the specification have been made to overcome this objection. In particular, Applicants submit herewith a copy of the specification as found on PAIR dated 10/21/87, wherein Applicants have changed the numbering such that pages now run consecutively from 1 to 44, and original pages including 9a-9d and 22a-22e have been replaced. Applicants have done this because they do not have in their position an electronic version of the original specification. Applicants hereby certify that the information in the attached specification includes no new matter.

D. The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). In this regard the Office Action states that correction of the following is required:

> Claims 60, 61, and 68 are directed to a process of diagnosing or classifying cancers in patients by detecting abnormal expression of a protein, which is encoded by a MAC117 gene, in "a body sample" acquired from the patient using an immunoassay. As evidenced by the declaration of Matthias H. Kraus under 37 C.F.R. § 1.132 filed June 17, 1996, the term "body sample" is not used solely to refer to a sample of tissue or tumor, since the body sample may instead be a sample of serum or effusion, or perhaps any other sample that might be acquired from the body of a patient, other than tissue or tumor cells. In contrast to the evident breadth of the term "body sample", as it is used in the context of the language of the claims, the descriptive portion of this

> application appears to describe only samples of tissue or tumor; the disclosure does not describe the use of samples of sera, effusions, or any other bodily component that might be acquired from the body of a patient, other than tissue or tumor cells. M.P.E.P. § 608.01(o) states:
> While an applicant is not limited to the. nomenclature used in the application as filed, he or she should make appropriate amendment of the specification whenever this nomenclature .is departed from by amendment of the claims so as to have clear support or antecedent basis in the specification for the new terms appearing in the claims. This is necessary in order to insure certainty in construing the claims in the light of the specification, Ex parte Kotler, 1901 C.D. 62, 95 O.G. 2684 (Comm'r Pat. 1901). See 37 CFR 1.75, MPEP § 608.01(i) and § 1302.01.
>
> MP.E.P. § 608.01(o) further states that if the examiner determines that the claims presented late in prosecution do not comply with 37 CFR 1.75(d)(1), applicant will be required to make appropriate amendment to the description to provide clear support or antecedent basis for the terms appearing in the claims provided no new matter is introduced.
>
> It is submitted that it would not be clear from a reading of the descriptive portion of this application, alone, where there is support for the language of the claims because apart from describing tissue samples and tumor cells, the disclosure fails to describe the "body samples" to which the claims are directed.

The claims no longer recite "body sample." This is believed to address this ground for rejection, such that its withdrawal is merited.

Claim Objections

Claims 61 (59) and 68 (66) are objected to because claims recite, "the 423 nucleotides set forth in Figure 1 or the restriction pattern set forth in Figure 5A". MP.E.P. § 2173.05(s) states:

> "Where possible, claims are to be complete in themselves. Incorporation by reference to a specific figure or table "is permitted only in exceptional circumstances where there is no practical way to define the invention in words and where it is more concise to incorporate by reference than duplicating a drawing or table into the claim. Incorporation by reference is a necessity doctrine, not for applicant's convenience." Ex parte Fressola, 27 USPQ2d 1608, 1609 (Bd. Pat. App. & Inter. 1993) (citations omitted).

The Office Action states that claims must, under modern claim practice, stand alone to define invention, and incorporation into claims by express reference to specification and/or drawings is not permitted except in very limited circumstances.

Claim 68 (66) is cancelled herein, thus mooting this rejection as to that claim.

For the reasons stated above, reference to a sequence identifier is not required in this application.

Claim Rejections – 35 USC § 101

Claim 69 (67) is rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility. In this regard the Office Action States the Following:

> 35 U.S.C. 101 reads as follows:
>
> > Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.
>
> The considerations that are made in determining whether a claimed invention is supported by either a specific and substantial asserted utility or a well-established utility are outlined by the published Utility Examination Guidelines (Federal Register; Vol. 66, No. 4, January 5, 2001). A copy of this publication can be viewed or acquired on the Internet at the following address: http://www..gpoaccess.gov/.
>
> Briefly, a "specific and substantial" asserted utility is an asserted, expressly identified utility that is specific to the particular nature and substance of the claimed subject matter, and which would be immediately available for application in a "realworld" context by virtue of the existing information disclosed in the specification and/or on the basis of knowledge imparted by the prior art, such that its use would not require or constitute carrying out further research to identify or reasonably confirm its usefulness in this context. A "well-established" utility is a credible, specific, and substantial utility, which is well known, immediately apparent, and implied by the specification, and based on the disclosure of the properties of a material or subject matter, either alone or taken with the knowledge of one skilled in the art.
>
> Claim 69 is drawn to a method of detecting a gene.
>
> The claim recites no intended use or purpose, however, apart from the detection of a gene.
>
> What specific and substantial utility or well established utility might such an invention have?
>
> In light of the disclosure, it appears that the claimed invention is not a useful process in and of itself, but rather a mere part of other disclosed processes that have asserted utilities.
>
> For example, claim 60 is directed to a process of diagnosing human cancer in a patient by detecting amplification of a MAC117 gene; and though it is very likely the detection of amplification of the gene necessarily involves the detection of the gene, it is not the presence of the gene alone that provides an indication that the gene is amplified. This is because the gene is expectedly present in every cell of the human body, though perhaps amplified in only a fraction of those cells. So, in order to detect amplification of the gene, the practitioner must not only detect the gene, but must quantify the gene.
>
> As such, it is not apparent that the specification asserts that the claimed invention itself has any specific and substantial utility; and it is not evident that it has any well established utility either.
>
> If the invention is actually only intended for use as an active step of some other process, rather than a useful process, in and of itself, having any one particular objective or purpose, the claim fails to meet the utility requirement set forth under 35 U.S.C. § 101.

> If not just a mere part of different useful inventions disclosed in this application, perhaps the claimed invention might be useful as an investigative tool, but Applicant is reminded that such an invention lacks the requisite specific and substantial utility of a patentable invention under 35 U.S.C. § 101.
>
> For example, the claimed invention might be used to make a determination that a cell contains a MAC117 gene that is detected using the invention, but because this would hold true of any process of detecting any gene, such utility is not a specific utility; and moreover, any benefit that might be derived by the public for a grant of a patent monopoly of the claimed process of detecting the disclosed gene is not specific to the nature of the process, or even to the substance and nature of the gene.
>
> Furthermore, based upon the information contained in the application, it would seem that there is no reason for detecting the presence of a MAC117 gene, apart from facilitating the objectives and aims of basic research directed toward the study of the function of the gene.
>
> In other words, given only the benefit of the existing disclosure of the invention, it is submitted that the claimed invention, in and of itself, cannot be regarded as having any immediate, practical, and beneficial utility.
>
> Notably, the idea of detecting a given gene by hybridizing a nucleic acid probe that anneals to the gene is not a novel concept; such processes have been practiced to detect genes since their original conception years ago.
>
> Furthermore, the gene to which the claim is directed is not novel, since the prior art teaches a gene encoding a polypeptide having the molecular weight of about 185 kDa, which is expressed, for example, by breast cancer cells3; so the idea of detecting a "MAC117 gene" is also not an original concept.

Claim 69 (67) as amended involves utility because it is directed to detection of amplification, which is useful in the clinical management of breast cancer patients. The claim is amended to make the comparison to normal breast tissue, since normal breast tissue would be the obviously relevant comparison in the context of the present claims.

Claim Rejections Under 35 U.S.C. § 112, second paragraph

Claims 60, 61, 68, and 69 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Particularly, claims 60, 61, 68, 69 are allegedly indefinite because the claims use of the designation "MAC117 gene" as the sole means of identifying the genes and/or other nucleic acids to which the claims refer. In this regard the Office Actions states the following:

> (a) Claims 60, 61, 68, and 69 are indefinite because the claims use of the designation "MAC117 gene" as the sole means of identifying the genes and/or other nucleic acids to which the claims refer.

In general, the use of laboratory designations only to identify a particular gene or nucleic acid molecule renders claims indefinite because different laboratories may use the same laboratory designations to define completely distinct genes and other nucleic acid molecules.

Indeed, in this case, it appears that other terms, such as "HER-2", "Neu", "c-ErbB-2" have been used in the art to identify the same gene or genes to which the claims may be directed.

Furthermore, it is aptly noted that the same term is often used in the art to describe, not one gene or nucleic acid molecule, but rather a plurality of genes (e.g., alleles, polymorphic variants, etc.), which are structurally and/or functionally related, but otherwise distinct. For example, the same term is often used to describe allelic variants, which encode structurally and/or functionally disparate proteins (i.e., "isoforms").

In addition, claims 60, 61, and 68 are directed to any of a plurality of "protein products" of the MCA117 gene, which may only be identified by the recited designation of the gene encoding those proteins. However, as explained, the use of laboratory designations only to identify a particular gene renders the claims indefinite because different laboratories may use the same laboratory designations to define completely distinct genes and/or other nucleic acid molecules, which encode structurally and/or functionally disparate proteins. Though such structurally and/or functionally different proteins are encoded by a single gene, they are the products resulting from translation of alternatively spliced transcripts of that gene.

In this case, there have been at least three isoforms described, which are encoded by a single "MAC117" gene, but are the translation products of differentially spliced transcripts; and it appears that each is expressed in different manners and extents by different types of cells, and that each may have substantially different specific activities and biologic functions.

Scott et al. (Mol. Cell. Biol. 1993 Apr; 13 (4): 2247-2257) describes an isoform, which although expected to be produced as a secreted variant of the cell membrane-bound "HER2 receptor", which contains only the extracellular ligand binding domain, is actually sequestered to within the cell; see entire document (e.g., the abstract).

Aigner et al. (Oncogene. 2001 Apr 19; 20 (17): 2101-2111) describes the expression of a similarly sized 100 kDa splice variant, which acts as an endogenous inhibitor of tumor cell proliferation; see entire document (e.g., the abstract).

Doherty et al. (Proc. Natl. Acad. Sci. USA. 1999 Sep 14; 96 (19): 10869-10874) has described a variant having a molecule weight of only about 68 KDa, which is encoded by a mRNA molecule that is expressed at reduced levels relative to mRNA encoding the 185 KDa isoform, which is often overexpressed in certain carcinoma cells containing the amplified gene; see entire document (e.g., the abstract). Unlike the larger 100 KDa isoform described by Scott et al. (supra), Doherty et al. teaches this isoform is secreted by cells; see, e.g., the abstract.

This position is further supported, for example, by the recent disclosure of Koletsa et al. (Neoplasia. 2008 Jul; 10 (7): 687-696). Koletsa et al. again teaches the "MAC117 gene" encodes a plurality of protein variants, which are the products of alternatively spliced mRNA molecules; see entire document (e.g., the abstract; and the paragraph bridging pages 687 and 688). Koletsa et al. teaches the better characterized isoform is encoded by a transcript that retains intron 8, such that the protein has a unique carboxy-tail sequence (paragraph bridging pages 687 and 688). Koletsa et al. teaches this isoform is a soluble protein, because it lacks a transmembrane domain, and can be secreted from cells (page 688, column 1). As might be expected in light of their different structures, Koletsa et al. teaches the soluble isoform appears to have functions that are

very unlike those of other isoforms, which are displayed at the surfaces of cells and not secreted; see, e.g., page 688, column 1.

Then, as final example of the reasons that the use of such nomenclature alone is insufficient to particularly point out and distinctly claim the subject matter that is regarded as the invention, it is noted that the same terms are frequently used to identify gene and/or the polypeptides encoded by those genes that occur in different species of animals; although sharing certain structural and/or functional characteristics, these genes and their products often have markedly distinct structures and/or functions (e.g., orthologs and paralogs).

35 U.S.C. § 112, second paragraph, requires the claim define the metes and bounds of the subject matter that is regarded as the invention with such clarity and particularity to permit the skilled artisan to know or determine infringing subject matter; because the terms used to describe the polypeptides to which the claims are directed do not unambiguously identify those polypeptides, this requirement has not been met.

Accordingly, it is suggested that this issue might be remedied by amending the claims to include a recitation of the nucleotide sequence of the gene or other nucleic acid molecules to which the claims are directed, or alternatively the amino acid sequence of the polypeptides encoded by those genes, by reference to one or more specific sequence identification numbers of corresponding to the same nucleotide or amino acid sequences as set forth in the Sequence Listing. This is because the nucleotide sequence of a nucleic acid molecule and the amino acid sequence of a polypeptide are unique identifiers that unambiguously define a given nucleic acid molecule and polypeptide, respectively.

Claims 68 (66) is cancelled, thus mooting this rejection as to that claim.

Claim 61 (59) currently recites structural characteristics of the MAC117 gene and protein product that distinguish what is referred to in the claims from other molecules, i.e., "wherein the MAC117 gene contains either a nucleotide sequence encoding the amino acids encoded by the 423 nucleotides set forth in Figure 1." Thus, one of skill in the art understands the metes and bounds of the claim with sufficient clarity to permit the determination of what is or is not be infringing subject matter.

Claims 60 (58) and 69 (67) are amended to recite structural characteristics of the MAC117 gene and protein product that distinguish what is referred to in the claims from other molecules. Thus, one of skill in the art understands the metes and bounds of the claim with sufficient clarity to permit the determination of what is or is not be infringing subject matter. Particularly, the claims recite "wherein the MAC117 gene contains either a nucleotide sequence encoding the amino acids encoded by the 423 nucleotides set forth in Figure 1 or the restriction pattern set forth in Figure 5A." Support for this amendment is found in claim 61 (59) and in the places where support for claim 61 (59) is found.

B. Claims 60, 61, and 68 are allegedly indefinite because the claims are directed to a method comprising detecting "increased" expression of a gene in a tissue or tumor cell sample of a patient. In this regard the Office Actions states the following:

> (b) Claims 60, 61, and 68 are indefinite because the claims are directed to a method comprising detecting "increased" expression of a gene in a tissue or tumor cell sample of a patient.
>
> The term "increased" is a relative term; yet, it cannot be ascertained relative to what standard the expression of the gene must be compared in practicing the process that is regarded as the invention, so as to determine if the level is increased in the tissue or tumor cell sample of the patient.
>
> The metes and bounds of the subject matter that is encompassed by the claims will vary widely, depending upon which standard value is used in the comparison; and the value of the standard might also vary substantially depending upon how it is determined.
>
> In accordance with a recent decision by the Federal Circuit (Halliburton Energy Services Inc. v. M-I LLC, 85 USPQ2d 1654, 1658 (Fed. Cir. 2008)):
>
> > 35 U.S.C. § 112, ¶ 2 requires that the specification of a patent "conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention." Because claims delineate the patentee's right to exclude, the patent statute requires that the scope of the claims, be sufficiently definite to inform the public of the bounds of the protected invention, i.e., what subject matter is covered by the exclusive rights of the patent. Otherwise, competitors cannot avoid infringement, defeating the public notice function of patent claims. Athletic Alternatives, Inc. v. Prince Mfg., Inc., 73 F.3d 1573, 1581 (Fed. Cir. 1996) ("[T]he primary purpose of the requirement is 'to guard against unreasonable, advantages to the patentee and disadvantages to others arising from uncertainty as to their [respective] rights.'") (quoting Gen. Elec. Co. v. Wabash Appliance Corp., 304 U.S. 364, 369, (1938)). The Supreme Court has stated that "[t]he statutory requirement of particularity and distinctness in claims is met only when [the claims] clearly distinguish what is claimed from what went before in the art and clearly circumscribe what is foreclosed from future enterprise." United Carbon Co. v. Binney & Smith Co., 317 U.S. 228, 236 (1942).
>
> The failure of the claims to make evident the value of the standard that must be applied, or the means by which that value is necessarily determined, render the claims indefinite; and moreover the metes and bounds of the subject matter that is regarded as the invention cannot be determined with the requisite clarity and particularity to satisfy the requirement set forth under 35 U.S.C. § 112, second paragraph, so as to permit the skilled artisan to know or determine infringing subject matter.

Claim 68 (66) is cancelled herein, thus mooting this rejection as to that claim.

One of skill in the relevant art will recognize that there are several standards relative to which the expression of the MAC117gene may be compared in practicing the process that is regarded as the invention, so as to determine if the level is increased in the tissue or tumor cell

sample of the patient. The specification provides numerous examples of these comparative measurements that provide the information necessary detect amplification or overexpression as recited in the claims. The fact that the method may be practiced in numerous ways, does not make the claim indefinite when the language of the claims and specification put the skilled person on notice as to the metes and bounds of the claim. As this is all that is required to satisfy 35 U.S.C. 112, second paragraph, the amended claim is also believed to free of the present rejection. There is no specific reason given by the Office as to why it views the language of the claims read in light of the teaching of the application to be insufficient to inform the skilled person as to the metes and bounds of the claims as currently pending. Thus, this ground for rejection is believed to be unsupported by any scientific basis, and as such, its withdrawal is respectfully requested.

Nevertheless, to advance prosecution, applicants have amended claims 60 (58) and 61 (69) to recite that the amplification or increased expression is relative to normal human breast tissue. The skilled person would unquestionably understand what is meant by normal human breast tissue. Thus, the metes and bounds of the claim are clear and put the skilled person on notice as to what acts would be infringing acts. As this is all that is required to satisfy 35 U.S.C. 112, second paragraph, the amended claim is also believed to free of the present rejection.

C. Claims 60 (58) and 68 (66) are allegedly indefinite because claim 60 (58) recites, "by hybridizing nucleic acid derived from a tissue or tumor cell sample of said patient with a nucleic acid probe of the MAC117 gene" and claim 68 (66) recites, "by hybridizing nucleic acid derived from a tissue or tumor sample containing cells from a patient diagnosed with cancer with a nucleic acid probe of the MAC117 gene." In this regard the Office Action further states the following:

> (c) Claims 60 and 68 are indefinite because claim 60 recites, "by hybridizing nucleic acid derived from a tissue or tumor cell sample of said patient with a nucleic acid probe of the MAC117 gene" and claim 68 recites, "by hybridizing nucleic acid derived from a tissue or tumor sample containing cells from a patient diagnosed with cancer with a nucleic acid probe of the MAC117 gene".
>
> It cannot be ascertained which "nucleic acid" is necessarily hybridized with the probe, or how that "nucleic acid" is necessarily derived from a tissue or tumor cell sample of the patient.
>
> Then, as explained in the rejections that follow, it is imperative that the type and nature of the "nucleic acid" be known in order to practice the claimed process in a manner that might achieve the intended result.
>
> Though the specification describes certain assays as utilizing particular types of nucleic acids, which are isolated from cells or tissues, Applicant is reminded that

> although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See In re Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).
>
> Thus, despite the disclosure, the claims cannot be unambiguously construed as encompassing any particular process that is described therein; and therefore the metes and bounds of the subject matter that is regarded as the invention cannot be determined with the requisite clarity and particularity to satisfy the requirement set forth under 35 U.S.C. § 112, second paragraph, so as to permit the skilled artisan to know or determine infringing subject matter.

Claim 68 (66) is cancelled, thus mooting this rejection as to that claim.

The Office seems to take the position that one of skill in the relevant art would not know that if amplification of a gene (any gene) is to be detected, that genomic DNA from the subject can be used for hybridization to detect copy number. Applicants strenuously disagree, but even if the Office will not give scientists this much credit, the application avoids any problem by exemplifying this method.

The Office also seems to take the position that one of skill in the relevant art would not know that if overexpression of the protein product of a gene (any gene) is to be detected 1) that mRNA from the subject can be used for hybridization (e.g., northern blot) to detect the amount of transcription (a typical correlate of translation/expression) or 2) that amounts of protein can be measured by electrophoretic techniques. Applicants strenuously disagree, but even if the Office will not give scientists this much credit, the application avoids any problem by exemplifying both methods.

There is no requirement that either the claims or the specification recite every way that a technical aspect of a claimed method can be practiced where, as here, the skilled person would recognize numerous ways to obtain the information that is at the heart of the claimed method.

D. Claim 60 (58) is indefinite because the claim recites the limitation, "the protein product of the MAC117 gene." In this regard the Office Action states the following:

> (d) Claim 60 is indefinite because the claim recites the limitation, "the protein product of the MAC117 gene". Because it would appear that there are a plurality of gene products encoded by the "MAC117 gene", since, for example, the human gene encoding the 185 kDa isoform is the same gene that encodes the 100 kDa isoform, it cannot be determined to which protein product of the gene the claims are directed. For this reason, the claim fails to delineate the metes and bounds of the subject matter that is regarded as the invention with the clarity and particularity necessary to satisfy the requirement set forth under 35 U.S.C. § 112, second paragraph.

Claim 60 (58) is amended herein to recite structural characteristics of the gene/protein product (i.e., the sequence) such that is clear what is being detected.

E. Claims 60 (58) and 61 (59) are allegedly vague and indefinite. In this regard the Office Action states the following:

> (e) Claims 60 and 61 are vague and indefinite because the claims recite the processes are intended for use in "classifying cancers", and though the processes comprise the step of "classifying those cancers from patients whose body samples show amplification or increased expression of said MAC117 gene or abnormal expression of the protein product of said MAC117 gene as being correlated with amplification of the MAC117 gene or increased expression of the protein product of the MAC117 gene", it is not evident what attributes or features of the cancers are "correlated" with gene amplification or increased expression of the gene product. A "correlation" is a reciprocal relation between two or more things. So, here, it is not understood how the cancers are actually classified upon practice of the claimed processes because it is not evident what relationship must be identified; but if it cannot be known whether or when the objective is met, it would seem that the claims necessarily fail to clearly and particularly point out the subject matter that is regarded as the invention, so as to permit the skilled artisan to know or determine infringing subject matter, and thereby satisfy the requirement set forth under 35 U.S.C. § 112, second paragraph.

Claim 60 (58) does not recited "classifying cancers." Thus, this rejection in not applicable to claim 60, and its withdrawal is respectfully requested.

Regarding claim 61 (59), it is not relevant what attributes or features of the cancers are "correlated" with gene amplification or increased expression of the gene product. The claim is directed to classifying cancers that evidence amplification of the MAC117 gene or overexpression of the MAC117 protein product. The only relationship that must be identified is the relationship between the cancer and the amplification of the MAC117 gene or overexpression of the MAC117 protein product by that cancer. Applicants' claimed method is not directed to the attributes or features of any cancer other than the fact that it evidences amplification of the MAC117 gene or overexpression of the MAC117 protein product. The claim defines what is classified by making the recited correlation. There is no reason given by the Office why it believes that the skilled person would read into the claim a requirement that is not there and need not be there to have a useful method. Thus, this ground for rejection should be withdrawn.

F. Claim 69 (67) is alleged to be too vague and indefinite to satisfy the requirement for clarity and particularity set forth under 35 U.S.C. § 112, second paragraph, for the following reasons stated in the Office Action:

> The claim is directed to an omnibus subject matter, as it is apparently directed to an active step (i.e., detecting a MAC117 gene), rather than a useful process having any one particular objective or purpose, which at first glance may conceivably be performed during any number of a vast plurality of objectively different processes.
>
> Indeed, the specification discloses a process for diagnosing cancer in a patient, which comprises detecting a MAC117 gene and determining, if the gene is amplified, rearranged and/or overexpressed, but the claimed process of detecting a MAC117 gene is not disclosed as having any particular purpose, in and of itself, and appears to be described as only an integral part or active step of other processes disclosed in this application.
>
> To satisfy the requirement set forth under 35 U.S.C. § 112, second paragraph, the claims must define the metes and bounds of the subject matter that is regarded as the invention by Applicant with the clarity and particularity necessary to permit the skilled artisan to know or determine infringing subject matter.
>
> What is the actual purpose or objective of practicing the process that is regarded as the invention? How and when not might the gene be detected by hybridizing nucleic acid with a nucleic acid probe of the gene without infringing the claim?

Claim 69 (67) is amended herein to be directed to detecting amplification of MAC117, and has the meaning based on the description of amplification in certain breast cancer cells.

Claim Rejections Under 35 U.S.C. § 112, first paragraph

Utility

Claim 69 (67) is rejected under 35 U.S.C. 112, first paragraph. In this regard the Office Action further states the following:

> Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.
>
> What is the actual "real-world" purpose or objective of practicing the invention? How is it to be used in a manner that would immediately benefit the public, and to what specific aim or objective?
>
> Inasmuch as the claimed invention has no requisite objective or purpose, apart from the detection of a gene, and has no apparent specific and substantial utility, in and of itself, the sufficiency of the disclosure to reasonably enable the skilled artisan to practice the' invention, or any objective process comprising the invention as an integral and active step cannot be assessed.
>
> Furthermore, because the claimed invention has no requisite, objective or purpose, apart from the detection of a gene, the claims merely serve as an invitation to elaborate a "real-world" use for the invention, or to develop a useful process comprising the active step of detecting the gene. However, any need to further elaborate or develop a utility for the claimed invention, which would satisfy the requirement set forth under 35 U.S.C. § 101, would constitute a need to perform undue and/or unreasonable experimentation.
>
> M.P.E.P. § 2164.01 states:

> The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of Mineral Separation v. Hyde, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That. standard is still the one to be applied. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).
>
> There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors, which have been outlined in the Federal Circuit decision of In re Wands, 858 F.2d 731,737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), include, but are not limited to, the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed. See also Ex parte Forman, 230 USPQ 546 (BPAI 1986).

Claim 69 (67) is amended as indicated above, and thus has the disclosed real world utility for detection of amplification of MAC117. This is believed to address this rejection, and its withdrawal is respectfully requested.

Written Description, new matter

Claims 61 (59), 68 (66), and 69 (67) are rejected under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the written description requirement. The Office Action asserts that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, and that this is a "new matter" rejection.

A. The Office Action notes that claims 61 (59) and 68 (66) are rejected directed to methods of classifying cancers. In this regard, the Office Action further states the following:

> Claim 61 was added by the amendment filed August 12, 1993. At page 3 of that amendment Applicant has remarked that specification "clearly supports that MAC117 amplification can be detected and used to classify those cancers having amplification".
>
> Thus, it would appear that it is Applicant's position that because the specification shows that the gene encoding the 185 kDa polypeptide is amplified in certain breast cancer cells, the specification must adequately support a claim directed to a method of classifying cancers.

It is argued however that since the specification shows that the gene encoding the 185 kDa polypeptide is amplified in certain breast cancer cells, the specification might adequately support a claim directed to a method of determining if the gene is amplified in breast cancer cells, but it would not support a claim directed to a method of classifying cancers.

Claim 68 was added by the amendment filed May 3, 2006; and at page 4 of that amendment Applicant has remarked that written support for the language of claim 68 is found in the specification at page 5, lines 3-6, and page 26, lines 23-25, if not also elsewhere.

The disclosure at page 5 reads as follows: "It is a still further object of the present invention to provide nucleic acid probes and/or antibody reagent kits capable of detecting said gene or a product thereof."

The disclosure at page 26 reads: "Having the knowledge of the gene allows preparing specific nucleic acid probes to detect the gene described here or its mRNA product."

Neither disclosure appears to provide written support for the claimed process of classifying cancers.

In fact, no where in the specification, as originally filed, are such methods expressly described.

Given the apparent absence of any express description of the claimed processes of classifying cancers, it is submitted that it is not evident what subject matter is actually regarded as the invention because, for example, it cannot be ascertained what objective must actually be met by "classifying" cancers or when that objective would be met. Presumably the claimed invention is not just a method of determining if the gene encoding the 185 kDa protein described in the application is amplified. Though this is arguably an issue better addressed under the provisions of 35 U.S.C. § 112, second paragraph, because it is not evident to what intent or purpose the invention is used, it is really not possible to determine if there might be any implied or inferred support found within the disclosure.

Even so, since the specification does not describe the "classification" of cancers the active process that is recited in the body of the claims, it seems unlikely that it would should be found to provide adequate written support, implied or otherwise, for the claimed methods of doing so.

Therefore, until established otherwise, it appears that the addition of claims 61 and 68, directed to methods of classifying cancers, has introduced new concepts, which might not be adequately supported by the specification, as originally filed; in which case the addition of those claims violates the written description requirement set forth under 35 U.S.C. § 112, first paragraph. This issue might be remedied if Applicant were to point to specific disclosures in the specification, including the claims, as originally filed, which are believed to provide the necessary written support for the language of the claims.

Claim 68 (66) is cancelled, thus mooting this rejection as to that claim.

Regarding claim 61 (59), applicants point out that the claim defines what is classified. Particularly, the claim recites "classifying those cancers from patients whose body samples show amplification or increased expression of said MAC117 gene or abnormal expression of the protein product of said MAC117 gene relative to normal human breast tissue as being correlated with amplification of the MAC117 gene or increased expression of the protein product of the

MAC117 gene." No more than this is claimed. Since this is what the application teaches, the specification puts this method into the hands of the skilled person.

In contrast, the rejection focuses on the tissue of origin of cancers that may be identified by the recited classification method. This issue is not relevant to the present claim as the claim does not recite any language that implicates this issue. The Office does not provide any explanation for why it believes that any requirement not present in the claims should be read into the claims. Since such a reading into the claim is the only apparent basis for this rejection, the rejection is improper. Thus, this ground for rejection should be withdrawn.

Nevertheless, to advance prosecution, claim 61 (59) is amended herein to recite a method of identifying breast cancers that show amplification of a MAC117 gene. Thus, any issues that arise related to the term "classifying" are now moot.

B. The Office Action notes that claim 69 (67) is directed to a method of detecting a MAC117 gene comprising hybridization with a nucleic acid probe gene. The Office Action further states the following:

> Claim 69 is not an original claim, but was added by the amendment filed May 3, 2006. At page 4 of that amendment Applicant has asserted written support for the claim is found in the specification, as originally filed, at page 5, lines 3-6, and at page 26, lines 23-25.
>
> The disclosure at page 5 reads as follows: "It is a still further object of the present invention to provide nucleic acid probes and/or antibody reagent kits capable of detecting said gene or a product thereof."
>
> The disclosure at page 26 reads: "Having the knowledge of the gene allows preparing specific nucleic acid probes to detect the gene described here or its mRNA product."
>
> Contrary to Applicant's assertion, however, it does not appear such disclosures provide adequate written support for the breadth of subject matter to which the instant claims are directed.
>
> Again, claim 69 is drawn to a method of detecting a gene; however, the claim recites no intended use or purpose, apart from the detection of the gene.
>
> Accordingly, this new claim is not directed to any of the originally disclosed and/or claimed processes that comprise the step of detecting the gene, but rather to an active step that might be comprised within any number of a very large plurality of objectively different processes, few of which might be described in the instant specification.
>
> Yet, no where in the specification does it appear the claimed invention (i.e., of detecting a MAC117 gene comprising hybridizing nucleic acid with a nucleic acid probe of the gene) is described, in and of itself.
>
> In fact, the only recitations of the term "detecting", which appear in the specification, are in descriptions of the products that are useful for detecting the gene and/or abnormalities thereof, or in descriptions of the processes that involve detection of the gene.

> For these reasons, it appears the addition of new claim 69 has introduced new concepts not adequately embraced by the contents of the specification, including the claims, as originally filed; and as such, addition of claim 69 has violated the written description requirement set forth under 35 U.S.C. § 112, first paragraph.
>
> This issue might be remedied if Applicant were to point to other particular disclosures in the specification, including the claims, as originally filed, which are believed to provide the necessary written support for the language of the instant claims.

Applicants traverse the present rejection. The rejection is based on the "breadth" of the claim. In its use of the term "breadth" the Office implies that the full scope of potential end uses of a method of detecting a nucleic acid must be supported in the specification. The Office Action also implies that the claim must recite its utility. There is no legal basis asserted for either of these requirements, and none is believed to exist. The fact that a claimed method or composition must have a utility is not properly expanded into a requirement that multiple uses be considered or recited. Also, there is no requirement that a claim recite its utility. For these reasons alone, the rejection is improper and should be with drawn.

The assertion that the claim is not directed to any of the originally disclosed and/or claimed processes, is not correct. It is hard to imaging how claim 69 is not directed to the use recited in the specification: "to provide nucleic acid probes and/or antibody reagent kits capable of detecting said gene or a product thereof." Such probes are used in the examples to detect MAC117. Thus, the claimed method is reduced to practice in the application. Even if end-uses of the claimed nucleic acid detection method are not disclosed, there is no per se enablement issue based on this as long as the claim does not recite that end use. As an illustration, it is clear that a method of maintaining normal blood sugar need not recite (and the application need not disclose) every use for that method as long as one use is disclosed or obvious. There is no assertion in the Office Action that the skilled person would not recognize that applicants were in possession of the claimed method. This because the claim is tied so closely to what applicants practiced in the examples.

Nevertheless, claim 69 (67) is amended herein to recite a method of detecting amplification of MAC117, which is relevant in the detection of breast cancer. This claim is believed to be enabled and have utility for the reasons stated above.

Written Description

A. Claims 60 (58), 61 (59), 68 (66), and 69 (67) are rejected under 35 U.S.C. 112, first paragraph, as

allegedly failing to comply with the written description requirement. In this regard the Office Action states the following:

> The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.
>
> This is a "written description" rejection.
>
> The considerations that are made in determining whether a claimed invention is supported by an adequate written description are outlined by the published Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, para. 1, "'Written Description" Requirement (Federal Register; Vol. 66, No. 4, January 5, 2001; hereinafter "Guidelines"). ...
>
> Thus, an original claim may provide written description for itself, but it must still be an adequate written description, which establishes that the inventor was in possession of the invention.
>
> In this instance, claim 60 is directed to a process for diagnosing any of a genus of "human cancers" in a patient by detecting amplification, rearrangement or increased expression of "a MAC117 gene" in a tissue or tumor cell sample from said patient; whereas claims 61 and 68 are directed to processes for classifying cancers by detecting amplification or increased expression of "a MAC117 gene" in a tissue or tumor sample containing cells from a patient diagnosed with cancer or alternatively by detecting abnormal expression of a protein product of said MAC117 gene; and claim 69 is directed to a process for detecting "a MAC117 gene".
>
> As such, each of claims 60, 61, 68, and 69 is directed to "a MAC117 gene", which is necessarily amplified, rearranged, or overexpressed in a tissue or tumor cell sample, so as to be indicative of the presence of human cancer in a patient from whom the sample is acquired.
>
> Notably the term "MAC117 gene" is not expressly defined in the specification, but is presumed to encompass a plurality of DNA molecules having different nucleotide sequences, including, for example, any gene comprising at least part of the nucleotide sequence recited in claim 1 (now canceled).
>
> As might be expected there are a very large number of structurally and functionally disparate genes comprising at least part of the nucleotide sequence that is recited in claim 1.
>
> It is submitted that the vast majority of such structurally and functionally disparate genes are not expected to have or bear any relationship to the gene that is described in this application as amplified and overexpressed in certain breast cancer cell lines (e.g., SK-BR-3).
>
> Accordingly the claims are broadly but reasonably directed to process for diagnosing any of a genus of "human cancers" in a patient by detecting amplification, rearrangement or increased expression of any of a very large number of structurally and functionally dissimilar genes in a tissue or tumor cell sample from said patient.
>
> In contrast to the breadth of claims 60, 61, 68, and 69, the specification merely describes the amplification and/or overexpression of a gene comprising the entirety of the nucleotide sequence recited in claim 1, which encodes a polypeptide having a molecular weight of about 185 kDa, in certain breast cancer cell lines; see, e.g., Figures 1 and 7.

The substantially more limited description of the particular gene comprising the entirety of the nucleotide sequence recited in claim 1 and encoding a polypeptide having a molecular weight of about 185 kDa would not reasonably convey to the skilled artisan that Applicant had possession of any of the claimed processes that comprise detecting amplification, rearrangement, or increased (abnormal) expression of any "MAC117 gene".

Just as the vast majority of the structurally and functionally disparate "MAC117 genes" are not expected to have or bear any relationship to the particularly described gene, it is also expected that few of such gene will be amplified and/or overexpressed in cancer cells, so as to suitable for use as diagnostic markers.

Then, even if the claims were substantially more limited to a gene comprising the entirety of the nucleotide sequence recited in claim 1, it is still submitted that the disclosure would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed for the following reasons:

The nucleotide sequence recited in claim 1 is described as that of a fragment of a cloned DNA molecule produced by cleavage of the molecule with the restriction enzymes Eco RI, Acc I and Nco 14; thus the sequence recited in claim 1 is but a mere portion of the entirety of the coding sequence of the cloned gene.

As such, even if the claims were directed to genes comprising the nucleotide sequence recited in claim 1, the genes would not necessarily comprise the nucleotide sequence of the cloned gene, which is amplified and/or overexpressed in certain breast cancer cell lines.

Figure 1 of the specification shows that the nucleotide sequence recited in claim 1 (i.e., the nucleotide sequence of the fragment of the cloned gene) comprises at two exons encoding at least part of a putative polypeptide having the amino acid sequences also depicted in Figure 1; thus the nucleotide sequence recited in claim 1 does not encode a full-length polypeptide.

As such, even if the claims were directed to genes comprising the nucleotide sequence recited in claim 1, the genes would not necessarily comprise the nucleotide sequence of the cloned gene that encodes a polypeptide of 185 kDa, which is recognized by the antibody described in this application.

Given the fact that the "MAC117 genes" encompassed by the claims have such widely varying structures and functions, it is submitted that the gene comprising the entirety of the nucleotide sequence recited in claim 1 and encoding a polypeptide having a molecular weight of about 185 kDa, which is described in this application, is not representative of the genus, as a whole, as the skilled artisan could not immediately envision, recognize, or distinguish at least a substantial number of the genes, even given the description of a restriction map of the cloned gene and part of its nucleotide sequence.

This is, in part, because the genes to which the claims are directed need not have or share any of particularly identifying structural features of the cloned gene, which account for any particularly identifying functional features of either the gene or its product, which are also shared by members of the claimed genus.

Applicant is reminded that "generalized language may not suffice if it does not convey the detailed identity of an invention." University of Rochester v. G.D. Searle Co., 69 USPQ2d 1886 1892 (CAFC 2004).

In this instance, there is no language that adequately describes at least a substantial number of members of the genus of genes to which the claims are directed, which are amplified, rearranged or overexpressed in cancer, so as to be useful in diagnosing the disease. A description of what a material must do, rather than of what it is, does not suffice to describe the claimed invention.

Again the gene, which is only described in part as comprising the nucleotide sequence recited in claim 1 and/or encoding the 185 kDa polypeptide, is not representative of the genus, as a whole, since members of the genus have widely varying structures and functions:

Furthermore, it aptly noted that the courts have established that the disclosure of a partial structure without additional characterization of the product may not be sufficient to evidence possession of the claimed invention. See, e.g., Amgen Inc. V. Chugai Pharmaceutical Co. Ltd, 927 F.2d at 1206, 18 USPQ2d at 1021 ("A gene is a chemical compound, albeit a complex one, and it is well established in our law that conception of a chemical compound requires that the inventor be able to define it so as to distinguish it from other materials, and to describe how to obtain it. Conception does not occur unless one has a mental picture of the structure of the chemical, or is able to define it by its method of preparation, its physical or chemical properties, or whatever characteristics sufficiently distinguish it. It is not sufficient to define it solely by its principal biological property, e.g., encoding human erythropoietin, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property. We hold that when an inventor is unable to envision the detailed constitution of a gene so as to distinguish it from other materials, as well as a method for obtaining it, conception has not been achieved until reduction to practice has occurred, i.e., until after the gene has been isolated.") (citations omitted).

Furthermore, the Federal Circuit has decided that a patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated. See Noelle v. Lederman, 69 USPQ2d 1508 1514 (CA FC 2004) (citing Enzo Biochem II, 323 F.3d at 965; Regents, 119 F.3d at 1568).

First of all, one cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483. Apart from the gene encoding the 185 kDa polypeptide, which is amplified and/or overexpressed in certain breast cancer cell lines, it seems improbable that Applicant conceived at least a substantial number of the other members of the claimed genus "MAC117 genes" that are amplified, rearranged, or overexpressed in human cancers, including those that encode, for example, any of the structurally and/or functionally disparate isoforms of the 185 kDa polypeptide that have since been described in the art.

Nevertheless, here, any alleged conception fails, not merely because the field is unpredictable or because of the general uncertainty surrounding experimental sciences, but because the conception is incomplete due to factual uncertainty that undermines the specificity of the inventor's idea of the invention. See Burroughs Wellcome Co. v. Barr Laboratories Inc., 40 F.3d 1223, 1229, 32 USPQ2d 1915, 1920 (Fed. Cir. 1994). Reduction to practice in effect provides the only evidence to corroborate conception (and therefore possession) of the invention.

Notably, too, Guidelines (supra) states, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (Id. at 1104). Guidelines further states, "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus" (Id. at 1106); accordingly, it follows that an adequate written description of a genus cannot be achieved in the absence of a disclosure of at least one species within the genus. Because the claims encompass a genus of variant species, an

adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. However, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; nor has Applicant shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; nor has Applicant described distinguishing identifying characteristics sufficient to show that Applicant had possession of the claimed invention at the time the application was filed.

For additional clarity it is appropriately noted that the structure of a gene cannot be instantly envisioned or predicted, even given a full description of a mRNA molecule, which is the transcript of the gene, or the cDNA molecule derived therefrom. A gene contains introns, or intervening sequences that are dispersed among the exons encoding the transcription and translation products of the gene. Introns do not provide coding information that is utilized in producing the RNA transcript or polypeptide encoded by a gene, and the polynucleotide sequences of the introns are excised during maturation of the RNA transcript, or mRNA so that only the polynucleotide sequences of the spliced exons remain. Therefore, the artisan cannot deduce the structure of an intron, or of a gene containing an intron given only the polynucleotide sequence of an mRNA molecule, or cDNA derived therefrom. In addition, a gene comprises polynucleotide sequences at either end, i.e., the 5' and 3' ends, which contain regulatory information. For example, the promoter of the gene is most commonly positioned at the 5' end of the gene and regulates the transcription of the gene. Because the polynucleotide sequence of the promoter of a gene is not transcribed, its structure cannot be surmised given only the polynucleotide sequence of the RNA transcript of the gene. Other regulatory sequences are positioned at the 5' and 3' ends of the gene, which encode portions of the RNA transcript, which are not translated.

As such, it is not possible to work backward from the known structure of a cDNA molecule, for example, to derive the unknown structure of the corresponding gene, which encodes the same polypeptide as the cDNA; and therefore, the structures of naturally occurring genes with regulatory elements, untranslated regions, and introns and exons can only be determined empirically. This position is supported, for example, by the disclosures of Harris et al. (J. Am. Soc. Nephrol 1995; 6:1125-1133), Ahn et al. (Nature Gen. 1993; 3: 283-291); and Cawthon et al. (Genomics 1991; 9: 446-460). In this particular case, only a portion of the nucleotide sequence of a single "MAC117 gene" is disclosed. As shown in Figure 1, it appears that this sequence comprises two exons and one intron, but is otherwise incomplete. Thus, the specification fails to fully describe the particularly identifying structural attributes of the gene.

M.P.E.P. § 2163.02 states, "[a]n objective standard for determining compliance with the written description requirement is, 'does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed'"

In addition, Applicant is reminded that the written description provision of 35 U.S.C § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the "written description" inquiry, whatever is now claimed.

Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (CAFC ;i991). See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993); Amgen Inc. v.

Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016 (CAFC 1991); University of Rochester v. G.D. Searle Co., 69 USPQ2d 1886 1892 (CAFC 2004).

Accordingly, it is submitted that in the absence of a detailed description of at least a substantial number of the members of genus of "MAC117 genes", one skilled in the art would not reasonably conclude that Applicant had possession of the claimed invention at the time the application was filed.

It is however important to note that the claims are directed, not to a product, but to a process of diagnosing cancer in patients, processes of classifying cancer, and processes of detecting a gene. Without the gene it is not possible to practice the claimed inventions, so as to achieve the claimed objectives.

Similarly it is not possible to practice the claimed invention, so as to achieve the claimed objective, if it is not known which types of cancer may be diagnosed by determining that the nucleic acid derived from a tissue or tumor cell contains an amplified, rearranged, or overexpressed MAC117 gene - but which types of cancer are those? As further discussed in the following paragraphs, it is apparently not every type of cancer that is associated with the amplification, rearrangement or overexpression of a MAC117 gene.

It would seem that the specification fails to describe with any of the requisite clarity and particularity the other types of cancer that may be diagnosed using the claimed process; and moreover, it fails to describe those types of cancer which may not.

It is aptly noted that the specification discloses that amplification of a MAC117 gene was only detected in some of the breast cancer cell lines analyzed; for example, amplification was detected in SK-BR-3 cells, but not in ZR-75-1 cells; see, e.g., Figure 8 B. Thus, it appears that only a portion of breast cancers are associated with amplification of a MAC117 gene.

Furthermore, although the specification describes certain breast cancer cell lines, such as SK-BR-3 and ZR-75-1 as containing an amplified and/or overexpressed MAC117 gene, it appears not to describe a single example of a cancer cell characterized as having a gene rearrangement. Instead the specification only vaguely discloses that the abnormalities of a MAC117 gene that might be detected in cells include gene rearrangement, which might be indicated by aberrantly migrating bands in hybridization based assays (page 29, lines 13-16); but since specification also expressly discloses that aberrantly sized mRNA was not detected in any cell (page 22a, lines 18-20), it is submitted that the skilled artisan would not reasonably conclude that Applicant had possession of the claimed process comprising detecting rearrangement of a MAC117 gene at the time the application was filed.

Claims 68 (66) is cancelled, thus mooting this rejection as to that claim.

It is clear from the application that applicants were in possession of a method for identifying breast/mammary cancers associated with the amplification of the gene designated MAC117 or associated with overexpression of the MAC117 gene product. The application demonstrates "gene amplification of MAC117 in 4 mammary tumor cell lines and the absence of MAC117 gene amplification in 4 other mammary tumor cell lines overexpressing MAC117 mRNA." (description of Figure 8). The finding that the MAC117 gene is amplified in a human mammary carcinoma indicates that alterations occur to this gene in human disease, e.g., breast

cancer.. The fact that some mammary tumors show amplification and others do not, is not relevant to claims to diagnosing cancer or classifying cancer, because the tumors that did not evidence amplification evidenced overexpression. The fact that some mammary tumor cell lines (e.g., MCF-7) do not show amplification of MAC117 or overexpress of the MAC117 gene product, does not mean that applicants are not in possession of a method for diagnosing or classifying breast cancers. A diagnostic method need not detect every instance of what it is diagnostic for in order to be useful.

Regarding claim 60 (58), as presently presented, this claim specifies that MAC117 contains a nucleic acid defined as encoding a specific amino acid sequence.

Regarding claim 61 (59), as presently presented, this claim specifies that MAC117 contains a nucleic acid defined as encoding a specific amino acid sequence.

Regarding claim 69 (67), as presently presented, this claim specifies that MAC117 contains a nucleic acid defined as encoding a specific amino acid sequence.

In the specification, the MAC117 gene is defined by reference to Figure 1 and Figure 5A. The description of Fig. 1 states that "Fig. 1 shows a characteristic fragment produced by Eco RI restriction of the cloned gene of the present invention: the restriction-site map of λMAC117 and plasmid pMAC117." This is sufficient to allow the skilled person to routinely detect this gene (and its amplification or overexpression) and to allow the skilled person to recognize that applicants were in possession of sufficient information about the gene to make it useful for breast cancer diagnostic and breast detection purposes.

There is no evidence to support the assertion that there are a very large number of structurally and functionally disparate genes comprising the nucleic acid disclosed in Fig. 1 or Fig. 5a. Thus, there is no support for the interpretation of claims 60 and 61 as being directed to diagnosing or classifying cancer by detecting amplification, re-arrangement or increased expression any of a large number of functionally or structurally disparate genes. The specification describes the amplification or overexpression of the gene defined in the claims and discloses its relevance to diagnosis or classification of breast cancer.

The fragment of MAC117 disclosed in Figure 1 can be used to detect the amplified or overexpressed gene associated with breast cancer. The specification states this repeatedly. Thus, the assertion that a gene defined this way would not necessarily comprise the sequence of the cloned gene or does not encode the full-length polypeptide is not relevant to the present

diagnostic and classifying claims. The specification teaches probes used to identify overexpression of the gene associated with cancer (see Fig. 6 and description of Fig. 6 among other places) and to identify amplification of the gene associated with cancer (see Fig. 8 and description of Fig. 8 among other places).

Regarding the relationship between the protein defined in Fig. 1 and the antibody that can be used to detect overexpression or abnormal expression of MAC117, Fig. 7 shows 'the 185-kDal protein specific for MAC117 and its overexpression in human mammary tumor cell lines. 45 μg total cellular protein was separated by electrophoresis and transferred to nitrocellulose filters. The protein was detected with an antipeptide antibody coupled to 125I protein A." The application further describes the antibody as follows: "Antisera were raised against a synthetic peptide whose sequence corresponded to a portion of the putative tyrosine kinase domain of MAC117" (Page 22b). Thus, the expectation would be that the sequence defined in Fig. 1 would be recognized by antibody to MAC117.

The statements in the Office Action that assert that the term "MAC117 genes" include nucleic acids with widely varying structures and function or that assert the absence of shared identifying structural features among the covered molecules, are not relevant to the claims currently presented. The specification defines the molecules of the currently presented claims in a manner that 1) distinguishes it from other materials and 2) describes how to obtain it. The specification shows how to identify (obtain) a new gene/nucleic acid and provides a distinguishing property (that it contains either a nucleotide sequence encoding the amino acids encoded by the 423 nucleotides set forth in Figure 1 or the restriction pattern set forth in Figure 5A). Similarly, actual reduction to practice of the nucleotide and protein sequence of Fig. 1 and antibody are demonstrated in the application. Thus the requirements for written description are met.

That the MAC117 gene's entire sequence is not instantly envisioned based on a disclosure of the mRNA/cDNA is not relevant to the present claims. Applicants are not claiming a gene. The present claims are directed to methods of detecting what is actually disclosed and making the disclosed diagnostic or classification correlation to breast cancer. It does not matter if a specific gene sequence is not disclosed or envisioned unless that is required to practice the claim. Furthermore, the sequence that is disclosed is sufficient to practice the methods because

hybridization using probes based on the Fig. 1 sequence detected amplification (or lack thereof) of MAC117 in certain cells and tissue.

Regarding isoforms of the 185 kDa polypeptide that have been identified subsequent to the filing of the present application, these are not relevant to the claims as currently amended. Thus, this rejection is believed to be overcome and its withdrawal is respectfully requested.

B. With regard to written description, the Office Action further states the following:

> Turning to a slightly different issue now, in further contrast to the claims, the only gene product (i.e., polypeptide) described in this application with any clarity and particularity is the 185 kDa polypeptide that is presumably encoded by the gene amplified and/or overexpressed in certain breast cancer cell lines; see, e.g., Figure 7.
>
> As shown in Figure 7 A, this 185 kDa polypeptide is produced by the breast cancer cell line SK-BR-3; it however not apparent produced by another cell line, namely A431, which is derived from a different type of cancer, a vulva epidermoid carcinoma.
>
> Thus, it is importantly noted that the gene encoding the 185 kDa polypeptide may not be expressed in all types of cancer, since it was not seen in a cell line derived from a vulva epidermoid carcinoma; yet, the claims are directed to a process for diagnosing any of a genus of "human cancers", and not necessarily breast cancer.
>
> The absence of the 185 kDa polypeptide in A431 epidermoid carcinoma cells suggests there is no basis for Applicant's assertion that the detection of amplification, rearrangement, or increased expression of a "MAC117 gene" in a sample of tissue or tumor acquired from a patient provides a diagnostic indication that the patient has any type of cancer.
>
> Instead it is submitted that at best the specification might show that there is a relationship between amplification and/or overexpression of the gene encoding the 185 kDa polypeptide in the cells contained in a sample of breast tissue from a patient and the presence of breast cancer in the patient.
>
> Otherwise, however, the specification would fail to reasonably convey to the skilled artisan that Applicant had possession of the claimed invention because it is apparent that not all types of cancer are associated with the amplification and/or overexpression of the gene encoding the 185 kDa polypeptide and there is no disclosed basis for reliably predicting whether any other types of cancer, apart from breast cancer, might be diagnosed upon detecting amplification and/or overexpression of the gene encoding the 185 kDa polypeptide in samples of breast tissue acquired from patients.
>
> Yet, it is further noted that although it appears the 185 kDa polypeptide is produced by both SK-BR-3 and ZR-75-1 breast cancer cell lines, it appears that Figure 7 B shows that little, if any, of the polypeptide is produced by the MCF-7 breast cancer cell line; if so, the specification would suggest that the expression of the gene encoding the 185 kDa polypeptide may not be a general attribute of breast cancer, which will be useful in diagnosing the disease, but may perhaps be a marker of some as then yet poorly defined subset of breast cancers.

Regarding the evidence that MAC117 gene product is produced in some breast cancer cell lines and little or none is produced in other breast cancer cell lines, this supports the relevance of the present methods. The currently claimed methods call for identifying breast

cancers that show amplification of a MAC117 gene or identifying breast cancers that show increased expression of a MAC117 gene product. This is only requires detection of a cancer as being correlated with amplification of the MAC117 gene or increased expression of the protein product of the MAC117 gene. The value of this method resides in the fact that some cancers will and some will not show amplification or overexpression, and the claimed method will identify which are which.

The currently claimed methods do not require that every or even a plurality of different protein products of the MAC117 gene be detected. Similarly, the claimed methods do not require that any or all rearrangements or other abnormalities of the MAC117 gene be detected. The teaching of the application is that the status of the MAC117 gene and its protein product provides useful information about the clinical status of a patient in which amplification or overexpression are detected. The application teaches that "[t]he determination of amplification in a human mammary carcinoma of the gene described here indicates that overexpression (or other abnormality) of the protein product of this gene is functionally important, thus diagnostically relevant" (page28). The Office does not appear to be challenging this teaching or the more specific teaching of the application that amplification or overexpression of the product of the MAC117 gene defined by references to Fig. 1 is indicative of breast cancer. This, by itself is a useful diagnostic method, and this is what is described. That there may be some cancers that are not detected by the claimed methods does not negate their usefulness. That the methods might not detect or classify a specific type or stage of breast cancer, does not mean that the method does not diagnose or classify cancer. To assert otherwise, the Office would have to take the nonsensical position that a diagnosis of stage III breast cancer is not a diagnosis of breast cancer. Since diagnosing or identifying breast cancer is what is claimed and what is described in the application, there is written description for what is claimed.

C. The Office Action raises an additional issue with regard to claims 60 (58), 61 (59), and 68 (66). In this regard the Office Action further states the following:

> Claims 60, 61, and 68 are directed to a process of diagnosing or classifying cancers in patients by detecting abnormal expression of a protein, which is encoded by a "MAC117 gene", in a body sample acquired from the patient using an immunoassay.
>
> It appears that written support for the concept of using such a body sample is found only in original claim 8 (now canceled), which recites a step of "detecting abnormal expression of the protein product of the gene of Claim 1 by

reacting a body sample of a human suspected of said cancer with antibodies of Claim 5". As noted in the above objections to the specification, there is however no antecedent basis for such claim language found in the disclosure.

As evidenced by the declaration of Matthias H. Kraus under 37 C.F.R. § 1.132 filed June 17, 1996, the term "body sample" is not used solely to refer to a sample of tissue or tumor, since the body sample may instead be a sample of serum or effusion, or perhaps any other sample that might be acquired from the body of a patient, other than tissue or tumor cells.

In contrast to the evident breadth of the term "body sample", as it is used in the context of the language of the claims, the specification appears to describe only samples of tissue or tumor; it does not describe the use of samples of sera, effusions, or any other bodily component that might be acquired from the body of a patient, other than tissue or tumor cells.]

Moreover, the specification fails to describe the presence of the 185 kDa polypeptide, or any isoform thereof, which is also encoded by a "MAC117 gene" in the serum or any other bodily fluid of patients with breast cancer or any other type of cancer. Instead the specification merely shows the presence of elevated levels of the polypeptide in the cellular extracts of certain breast cancer cell lines; see, e.g., Figure 7 B; and page 22b, lines 4-15, of the originally filed specification.

The art teaches that the presence of a tumor-associated antigen in the serum or other bodily fluid of the patient afflicted by cancer cannot be predicted solely upon the basis that the antigen is abnormally expressed at relatively abundant levels by the cancer.

Claim 68 (66) is cancelled herein, thus mooting this rejection as to that claim.

None of currently amended claims 60 (58), 61 (59) and 69 (67) recite "body sample." Thus, this ground for rejection is overcome, and its withdrawal is respectfully requested.

Enablement

Claims 60 (58), 61 (59), and 68 (66) are rejected under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the enablement requirement. In this regard the Office Action Further states the following:

> The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.
>
> M.P.E.P. § 2164.01 states:
>
> > The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of Mineral Separation v. Hyde, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and

use the invention without undue experimentation. In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

There .are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors, which have been outlined in the Federal Circuit decision of In re Wands, 858 F.2d 731,737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), include, but are not limited to, the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed. 1986).

The amount of guidance, See also Ex parte Forman, 230 USPQ 546 (BPAI direction, and exemplification disclosed in the specification, as flied, would not be sufficient to enable the skilled artisan to use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

As explained in the above rejection of the claims as failing to satisfy the written description requirement, it is evident that the claimed invention could not be used without undue and/or unreasonable experimentation.

Applicant is therefore reminded that reasonable correlation must exist between the scope of the claims and scope of enablement set forth. In deciding In re Fisher, 166 USPQ i8, 24 (CCPA 1970), the Court indicated the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. "Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention." Genentech Inc. v. Novo Nordisk A/S, 42 USPQ2d 1001, 1005 (CAFC 1997).

Thus, the overly broad scope of the claims would merely serve as an invitation to one skilled in the art to determine which types of cancer, if any, might be diagnosed (or classified) by determining if "a MAC117 gene" is amplified, rearranged or overexpressed.

Though the specification describes the amplification of a gene in one breast cancer cell line, it describes the lack of amplification of the gene in another breast cancer cell.

Though the specification describes the overexpression of a .gene in a breast cancer cell line, it describes the lack of expression in another.

Yet, the claims are not limited to processes for diagnosing breast cancer, but are instead directed to processes for diagnosing any of a genus of human cancers.

Despite this fact, the specification teaches that the gene that is amplified and/or overexpressed in certain, but not all breast cancer cells is neither amplified nor overexpressed in an epidermoid carcinoma.

Then, as evident in view of later published studies, it would seem that the gene is only associated with a proportion of adenocarcinomas, but few if any other types of cancer.

Moreover, it appears that the amplification and/or overexpression of the gene in breast cancer may not be diagnostic of early stage disease, but is instead better suited for use as a prognostic marker predictive of relapse and overall survival.

The specification does not describe any gene rearrangement, nor does it attribute the presence of any cancer to the occurrence of a gene rearrangement.

Claims 60 (58), 61 (59), and 69 (67) as amended above should be reconsidered with regard to the present grounds for rejection. Applicants have traversed the written description rejections referred to in this rejection above. Thus, for the several grounds for rejection that the Office Action reasserts in this rejection, applicants' remarks are reasserted herein by reference. In the interest of efficiency, each ground of rejection and response is not necessarily repeated here.

The specification teaches how to detect amplification of MAC117 and overexpression of the MAC117 gene product. Each of these methods is actually reduced to practice in an Example. Thus, the application explicitly teaches how to detect amplification using a probe, and explicitly teaches how distinguish between MAC117 amplification and the normal complement of the gene. The skilled person would also recognize that the exemplified method is effective. The application explicitly teaches how to detect overexpression, for example by using an antibody to the protein product. The relevance of amplification or overexpression to the claimed diagnosis or classification methods is demonstrated in the application.. Having reduced these methods to practice, there enablement is established.

Regarding, the detection of rearrangements, the claims do not require this; thus, its enablement is not required.

Claim Rejections – 35 USC § 102

A Claims 60, 61, 61, 68, and 69 are rejected under 35 U.S.C. 102(b) as allegedly being anticipated by King et al. (Science. 1985 Sept 6; 229: 974-976). In this regard the Office Action further states the following:

> Herein, claims 60, 61, and 68 are drawn to a process comprising determining whether a MAC117 gene is amplified in a tissue or tumor cell from a patient by hybridizing nucleic acid derived from the tissue or tumor cell with a nucleic acid probe of the gene; and claim 69 is drawn to a process of detecting a MAC117 gene by hybridizing nucleic acid with a nucleic acid probe of the gene.
>
> King et al. teaches a process comprising detecting a gene and determining that the gene is amplified in the human mammary carcinoma cell line, MAC117 by hybridizing nucleic acid derived from the cells with a nucleic acid probe of the gene; see entire document (e.g., the abstract; and page 974, Figure 1 and column 3). More particularly, King et al. discloses that a probe consisting of a 1 kbp restriction fragment of the cloned gene was used to detect and quantify a 6 kb Eco RI fragment of the gene; see, e.g., page 974, Figure 1. King et al. teaches that the results of the analysis indicated that the gene was amplified in nucleic acid derived from the MAC117 cells (page 974, column 3).
>
> As apparent from the disclosure of King et al., the cloned gene that was amplified in the nucleic acid of MAC117 cells contains a nucleotide sequence encoding the amino

> acids encoded by the 423 nucleotides set forth in Figure 1 of this application; see page 975, Figure 2.
>
> Although it does not appear that King et al. describes classifying the cancer cells, as explained in the above rejection of the claims as failing to satisfy the requirement set forth under 35 U.S.C. § 112, second paragraph, it is not evident how the cancer must be classified, or what the active step of classifying the cancer actually entails, since it cannot be ascertained which attributes or features of the cancers to be classified are correlated with gene amplification or increased expression of the gene product. A "correlation" is a reciprocal relation between two or more things; and as such, it is not understood how the cancers must be classified because it is not apparent what relationship must be identified. For this reason, it cannot be known whether or when the objective of the claimed process is met, or whether or not any given process described by the prior art involves such an active step. Therefore, until shown otherwise, it is submitted reasonable to deem that the process disclosed by King et al. is materially and manipulatively indistinguishable from the claimed process.
>
> Receipt of the declaration under 37 C.F.R. § 1.131 by C. Richter King, Matthias H. Kraus and Stuart A. Aaronson, which was filed on June 17, 1996, is acknowledged; however, this rejection is made under 35 U.S.C. § 102(b) and Applicant is reminded that a rejection under § 102(b) cannot be overcome by affidavits and declarations under § 1.131. See M.P.E.P. § 2133.02. Accordingly, any consideration of the merit of the declaration is present moot.

Claim 68 (66) is cancelled herein, thus mooting this rejection as to that claims.

The present application claims priority to Application No. 06/836,414, which was filed March 5, 1986 for claims 60 (58) and 61 (59). The filing date of the priority application is less than one year from the publication of King et al., which is a publication of the inventors.

The present application is entitled to priority to the parent filing date. The Office Action describes claims 60 (58), 61 (59) and 69 (66) as "drawn to a process comprising determining whether a MAC117 gene is amplified in a tissue or tumor cell from a patient by hybridizing nucleic acid derived from the tissue or tumor cell with a nucleic acid probe of the gene." The parent application discloses at least this process, i.e. it discloses MAC117, how to measure its amplification by probe hybridization, and that it is amplified in mammary tumor cells from a patient. The parent application describes the invention in the Technical Field: "identification of a v-erbB related human gene that is a new member of the tyrosine kinase encoding family of genes and is amplified in a human mammary carcinoma." The v-erbB related gene is MAC117, and the application discloses its amplification and the association of the amplification with cancer:

> The finding that the gene described here is amplified in a human mammary carcinoma indicates that alterations occur to this gene in human disease. Thus, detection of the amplification of this gene provides useful diagnostic tools for the

detection and treatment of human mammary carcinoma or other malignancies resulting from Verb-B related gene.

The specification and drawings of the priority application disclose amplification of the MAC117 gene in mammary tumor cells. For example, the specification teaches the following:

> DNA prepared from tissue of a human mammary carcinoma, MAC117, showed a pattern of hybridization that differed both from that observed with DNA of normal human placenta and from that observed with the A431 sequmous-cell carcinoma line, which contains amplified epidermal growth factor (EGF) receptor genes. In A431 DNA, four Eco RI fragments were detected that had increased signal intensities compared to those of corresponding framents in placenta DNA (Fig. 1A). In contrast, MAC117 DNA contained a single 6-kilobase pair (kbp) fragment, which appeared to be amplified compared to corresponding fragments observed in both A431 and placenta DNA's. (page 19, lines 8-20);
>
> By digestion of pMAC117 with Bgl I and Bam HI, it was possible to generate a single-copy probe homologous to v-erbB. This probe detected a 6-kb Eco RI fragment that was amplified in MAC117 DNA and apparently increased in A431 cellular DNA relative to normal DNA (Fig. 1B). The sizes of the fragment corresponded to the amplified 6-kb Eco RI fragment detected in MAC117 DNA by means of v-erbB (Fig. 1A). Hybridization to Southern blots containing serial dilutions of MAC117 genomic DNA indicated an approximate amplification of 5- to 10-fold when compared to human placenta DNA. (page 20, lines 1-20);
>
> [A] five-to tenfold amplification of a v-erbB-related gene in the MAC117 mammary carcinoma made it possible to identify this sequence against a complex pattern of EFG receptor gene fragments. (page 22, lines 7-11); and
>
> The five- to tenfold amplification of the v-erbB-related gene of the present invention in a mammary carcinoma indicates that increased expression of this gene may have provided a selective advantage to this tumor. (page 23, lines 19-23).

Fig. 2 of the parent application discloses that MAC117 is amplified in mammary tumor cells. It is noted that the some of the references to Fig. 1A and Fig. 1B in the specification of the parent application should refer to Fig. 2 and vice versa. This is an obvious error as it is clear from the figures and from the context of the references to them which references should be to which figures.

Thus, a process comprising determining whether a MAC117 gene is amplified in a tissue or tumor cell from a patient by hybridizing nucleic acid derived from the tissue or tumor cell with a nucleic acid probe of the gene is disclosed in the parent application. This teaching allows

the detection of amplification and overexpression of the MAC17 gene or its product and, thereby, allows the identification of a tumor having amplification of the MAC117 gene or overexpression of its protein product for this reason, the present claims are entitled to priority in the parent application. Because the King et al. reference is a publication of the inventors, and is less than 1 year prior to the priority filing date of the present application, this reference is not properly cited against the present application.

Furthermore, since the parent application supports claims 60 (58), 61 (59), and 69 (67) of the present application, the present application is entitled to the priority date of the parent application, March 5, 1986. Because King et al. was published on September 6, 1985, less than one year prior to the filing date of the parent application, the present rejection is not properly a 102(b) rejection. Since the present rejection is not a 102(b) rejection, applicants' Declaration under 37 C.F.R. § 1.131 by C. Richter King, Matthias H. Kraus and Stuart A. Aaronson is applicable, and overcomes the present rejection.

Furthermore, the specification of the priority application is co-extensive with the disclosure of King et al. (Science 1985, Sept. 6, 229:974-976). Thus, for the same reason that King et al. would be anticipatory if more than one year prior to the priority date, the present application in entitled to priority to the parent application. Because the King et al. reference is a publication of the inventors, and is less than 1 year prior to the priority filing date of the present application, this reference is not properly cited against the present application. Thus, withdrawal of this ground for rejection is believed to be merited and is respectfully requested.

B. Claims 60 (58), 61 (59), 68 (66), and 69 (67) are rejected under 35 U.S.C. 102(b) as being anticipated by Coussens et al. (Science. 1985 Dec 6; 230:1132-1139). In this regard the Office Action further states the following:

> Herein, claims 60, 61, and 68 are drawn to a process comprising detecting a MAC117 gene in a tissue or tumor cell by hybridizing nucleic acid derived from the tissue or tumor cell with a nucleic acid probe of the gene. This interpretation of the claims is considered reasonable since the claimed process is need not be practiced using tissues or tumor cells that necessarily contain amplified, rearranged, or overexpressed genes. Thus, the claims do not necessitate the detection of amplification, rearrangement or overexpression of a MAC117 gene; instead the claims simply require that a process comprise the step of hybridizing nucleic acid derived from the tissue or tumor cell with a nucleic acid probe of the gene. Claim 69 is drawn to a process of detecting a MAC117 gene by hybridizing nucleic acid with a nucleic acid probe of the gene.
>
> Coussens et al. teaches a process comprising hybridizing nucleic acid derived from the tissue or tumor cell with a nucleic acid probe of the gene; see entire document (e.g., page 1134, Figure 2; and page 1137, Figure 5). More particularly, Coussens et al.

teaches a Northern blot analysis of nucleic acid derived from normal and malignant tissues, which was performed using two different probes of the gene, which consisted of restriction fragments of cloned cDNA molecules that were derived from transcripts of the gene; see, e.g., page 1134, Figure 2. In addition, Coussens et al. teaches a Southern blot analysis of nucleic acid derived from human lymphoblastoid cells, mouse 3T3 cells, and various somatic cell hybrids of cells from humans and rodents using the same probes; see, e.g., page 1137, Figure 5.

As apparent from the disclosure of Coussens et al., the cloned gene that was amplified in the nucleic acid of various tissues or tumor cells contains a nucleotide sequence encoding the amino acids encoded by the 423 nucleotides set forth in Figure 1 of this application; see page 1135, Figure 3.

Although it does not appear that King et al. describes classifying the cancer cells, as explained in the above rejection of the claims as failing to satisfy the requirement set forth under 35 U.S.C. § 112, second paragraph, it is not evident how the cancer must be classified, or what the active step of classifying the cancer actually entails, since it cannot be ascertained which attributes or features of the cancers to be classified are correlated with gene amplification or increased expression of the gene product. A "correlation" is a reciprocal relation between two or more things; and as such, it is not understood how the cancers must be classified because it is not apparent what relationship must be identified. For this reason, it cannot be known whether or when the objective of the claimed process is met, or whether or not any given process described by the prior art involves such an active step. Therefore, until shown otherwise, it is submitted reasonable to deem that the process disclosed by Coussens et al. is materially and manipulatively indistinguishable from the claimed process.

Receipt of the declaration under 37 C.F.R. § 1.131 by C. Richter King, Matthias H. Kraus and Stuart A. Aaronson, which was filed on June 17, 1996, is acknowledged; however, this rejection is made under 35 U.S.C. § 102(b) and Applicant is reminded that a rejection under § 102(b) cannot be overcome by affidavits and declarations under § 1.131. See M.P.E.P. § 2133.02. Accordingly, any consideration of the merit of the declaration is present moot.

Claim 68 (66) is cancelled herein, thus mooting this rejection as to that claim.

As the Office states in the rejection over King et al., the present claims are "drawn to a process comprising determining whether a MAC117 gene is amplified in a tissue or tumor cell from a patient by hybridizing nucleic acid derived from the tissue or tumor cell with a nucleic acid probe of the gene."

The parent application discloses at least this process, i.e. it discloses MAC117, how to measure its amplification by probe hybridization, and that it is amplified in mammary tumor cells from a patient. A detailed description of the evidence that the present claims are supported in the parent application is provided above. Since the parent application supports claims 60 and 61 of the present application, the present application is entitled to the priority date of the parent application, March 5, 1986. Because Coussens et al. was published on December 6, 1985, less than one year prior to the filing date of the parent application, the present rejection is not

properly a 102(b) rejection. Since the present rejection is not a 102(b) rejection, applicants' Declaration under 37 C.F.R. § 1.131 by C. Richter King, Matthias H. Kraus and Stuart A. Aaronson is applicable, and overcomes the present rejection. Since the presented Declaration establishes a date of invention prior to the publication date of Coussens et al., withdrawal of this ground for rejection is believed to be merited and is respectfully requested.

Furthermore, it is not proper to characterize the same claims differently depending on what art is being applied. Thus, the materially different interpretation of the claims recited in the present rejection over Coussens et al. compared to the interpretation recited in the rejection over King et al. is improper. Thus, the present rejection, which is admittedly based on that interpretation, is improper. Its withdrawal for this reason alone is believed to be merited.

The statement that the claimed process need not be practiced using tissues or tumor cells that necessarily contain amplified, rearranged, or overexpressed genes does not make sense based on the language of the claims. Each of the pending claims recites detection of amplification or detection of increased expression (overexpression). Since Coussens et al. does not disclose detection of amplification or increased expression, they do not anticipate claims 60 (58), 61 (59), 69 (67) or new claims 68-70.

Coussens et al. does not disclose overexpression or amplification in any tissue. Furthermore, it does not mention expression in breast tissue of any status. Thus, it cannot anticipate a method that is directed to detection of amplification or overexpression in cancer patients.

C. Claims 60 (58), 61 (59), 68 (66), and 69 (67) are rejected under 35 U.S.C. 102(e) as allegedly being anticipated by U.S. Patent No. 4,968,603-A (of record; cited by Applicant). In this regard the Office Action further states the following:

> Herein, claims 60, 61, and 68 are drawn to a process comprising determining whether a MAC117 gene is amplified or overexpressed in a tissue or tumor cell from a patient by hybridizing nucleic acid derived from the tissue or tumor cell with a nucleic acid probe of the gene, or alternatively by contacting cellular extracts of the tissue or tumor cell with an antibody that specifically binds to the protein encoded by the gene in an immunoassay; and claim 69 is drawn to a process of detecting a MAC117 gene by hybridizing nucleic acid with a nucleic acid probe of the gene.
>
> U.S. Patent No. 4,968,603-A (Slamon et al.) teaches a process comprising determining whether a gene, which is designated "HER2/neu", is amplified in a tissue or tumor cell from a patient by hybridizing nucleic acid derived from the tissue or tumor cell with a nucleic acid probe of the gene; see entire document (e.g., the abstract). Slamon et al. discloses that amplification of the gene is related to the status of neoplastic diseases, particularly breast adenocarcinomas; see, e.g., the abstract. Slamon et al. further discloses

since gene expression corresponds to gene amplification that alternatively gene expression may be measured based on the level of mRNA transcription and/or gene product; see, e.g., column 3, lines 52-54. Slamon et al. teaches mRNA transcription can be measured by a variety of techniques, including Northern blotting, and that a variety of methods for measuring expression of the gene product exist, including Western blotting and immunohistochemical staining; see, e.g., column 3, line 52, through column 4, line 40.

Slamon et al. discloses that the gene that was amplified in the nucleic acid of breast tumor cells, for example, was independently isolated by other research groups and has been designated "MAC117" by one of these groups; as such, it would appear that the gene described by Slamon et al. is the same as the gene to which the claims are directed (i.e., a gene that contains a nucleotide sequence encoding the amino acids encoded by the 423 nucleotides set forth in Figure 1 of this application).

Receipt of the declaration under 37 C.F.R. § 1.131 by C. Richter King, Matthias H. Kraus and Stuart A. Aaronson, which was filed on June 17, 1996, is acknowledged; however, the declaration is ineffective to overcome this ground of rejection because: (a) it fails to establish that the acts were performed in this country; and (b) the scope of the declaration is not commensurate with the scope of the claims.

In particular regard to the latter reason the declaration is deemed insufficient, it is noted that the declaration provides, as evidence of an alleged reduction to practice of the claimed invention, a copy of the publication of King et al. However, while the claims are directed to a process for diagnosing any of a genus of human cancers, King et al. discloses only their detection of the amplification of a novel v-erbB-related gene in MAC117 breast cancer cells, pointedly indicating that "extensive studies will be required to determine the frequency of MAC117 gene amplification in different human malignancies" (page 975, column 1). Moreover, King et al. discloses that the gene was not amplified in A431 vulva epidermoid carcinoma cells (page 974, Figure 1) and that"[a]nalysis of DNA from ten additional mammary carcinomas has not revealed amplification of the MAC117 gene" (page 975, column 1); so it seems that King et al. fails to establish that amplification of the gene in the MAC117 cell line was little more than anomaly. Furthermore, King et al. shows no evidence of either rearrangement of the gene or its overexpression in MAC117 breast cancer cells or any other cells. Such considerations support the position that the scope of the declaration is not commensurate with the scope of the claims.

Claim 68 (66) is cancelled herein, thus mooting this rejection of that claim.

With regard to where the activities noted in the Declaration took place, applicants note that all inventors did this work while at the NIH. However, applicants are willing to submit a revise declaration that states this explicitly. Thus, attached hereto for the Examiner's consideration of its content is an unsigned copy of the revised declaration that explicitly states that inventive activities embodied in the King et al. publication all took place in the United States. Applicants believe that with the consideration of this document, the signed version of this declaration can be submitted shortly without presenting any new issues.

With regard to the scope of the Declaration vis-à-vis the scope of the claims, the currently amended claims recite breast cancer, and are not subject to interpretation as disclosing a genus of human cancers. There is evidence in the form of data establishing amplification of MAC117 in breast cancer cells. The Office appears to agree with this where it states the following:

> As apparent from the disclosure of King et al., the cloned gene that was amplified in the nucleic acid of MAC117 cells contains a nucleotide sequence encoding the amino acids encoded by the 423 nucleotides set forth in Figure 1 of this application; see page 975, Figure 2.

Thus, the Declaration establishes that the invention of claims 60 (58), 61 (59), 69 (67) took place prior to the publication of Slamon et al. Overexpression is a typical correlate of amplification, such that the disclosure of amplification is could be reasonably expected to result in increased expression. Thus, the data in the Declaration show that the invention of claims 68-70 was invented prior to the publication date of Slamon et al. Thus, withdrawal of this rejection and allowance of the claims is believed to be merited.

Please charge Deposit Account No. 14-0629 in the amount of $1110.00, representing the fee for a large entity under 37 C.F.R. § 1.17(a)(3), and a Three-Month Extension of Time are enclosed. This amount is believed to be correct; however, the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

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